IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Applicant:	)	John A. Hamilton
Serial No.:	)	09/851,230
Filing Date:	)	May 8, 2001
Group Art Unit:	)	1644
Examiner:	)	Belyavskyi, Michail A.
For:	)	A Method for the Treatment and Prophylaxis of Inflammatory Conditions

DECLARATION UNDER 37 C.F.R. § 1.131

We, John A. Hamilton and Gary P. Anderson, declare that:

1.   We are joint inventors of the subject matter of the above-identified patent application (the "'230 application"); the contents of the application are well known to us and we have read the Office Actions dated August 10, 2005 and March 28, 2006 as well as U.S. Patent Application Publication No. US2000-0141994 to Devalaraja, *et al.* (the "994 Publication").

2.   We carried out, or caused to be carried out at our direction and under our supervision, certain experimental work which demonstrates that the invention of the '230 application was completed prior to March 20, 2000.

3.   A red number has been added in the lower left hand corner of the attached notebook pages to facilitate reference thereto. The dates have also been redacted. No other changes have been made to the original documents.

4.   The experimental work described herein occurred prior to March 20, 2000. Scientific data evidencing the conception and reduction to practice of the present invention from

the contents of attached Exhibit 1. The data come from our scientific laboratory notebooks and demonstrate that antibodies specific to GM-CSF are capable of ameliorating the effects of inflammation in a mouse by inhibiting or antagonizing the effects of GM-CSF on cells of the monocyte/macrophage lineage.

5.   We observed that mice with a knockout mutation in GM-CSF (GM-CSF -/-) demonstrated a significantly reduced incidence of arthritis compared to wild-type mice (GM-CSF $^{+/+}$) or heterozygous mice (GM-CSF $^{-/+}$). This indicated that inhibiting GM-CSF could be a means of treating or preventing inflammation. Based thereon, we conducted experiments to use antibodies to specifically inhibit GM-CSF.

6.   DBA\1 mice were injected with type II collagen (CII) in Freund's Complete Adjuvant (FCA) to induce arthritis (Exhibit 1, top of p.1). After appearance of arthritis, these mice (10 per group) were either treated with 22E9, a neutralizing monoclonal antibody specific for GM-CSF or an isotype control (Exhibit 1, middle of p.1). The clinical score was monitored daily to ascertain the level of inflammatory arthritis present within the two groups of animals. As seen in Figure 1 (Exhibit 1, p. 3), animals which were treated with the 22E9 monoclonal antibody specific for GM-CSF developed significantly lower levels of disease than those treated with the isotype control.

7.   Attached Exhibit 2 contains data from our scientific laboratory notebooks that demonstrate that antibodies specific for M-CSF are capable of ameliorating inflammatory arthritis in a mouse by inhibiting or antagonizing the effect of M-CSF on cells of the monocyte/macrophage lineage.

8.   We observed that mice with a mutation rendering M-CSF inactive demonstrated significantly reduced arthritis compared to wild-type mice. This indicated that inhibiting M-CSF

could be a means of treating or preventing inflammation. Based thereon, we conducted experiments to use antibodies to specifically inhibit M-CSF.

9. DBA/1 mice were injected with CII in FCA to induce arthritis as described on page 1 of Exhibit 2. At day 27, mice exhibiting signs of arthritis were divided into 2 groups of 10 and injected with either 5AI, a monoclonal antibody specific for M-CSF, or an isotype control antibody, DX48. The clinical score was monitored daily to ascertain the level of inflammatory arthritis present within the two groups of animals. As seen in Figure 2 (Exhibit 2, page 3), animals treated with the 5AI monoclonal antibody specific for M-CSF developed significantly lower levels of disease than those treated with the isotype control.

10. Accordingly, prior to March 20, 2000, we demonstrated that antibodies specific for GM-CSF or M-CSF are capable of ameliorating the effects of inflammation in a subject by inhibiting or antagonizing the effects of GM-CSF or M-CSF on cells of the monocyte/macrophage lineage.

11. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge the willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: _22nd June, 2006_   _____
                                        John A. Hamilton

Date: _22nd June, 2006_   _____
                                        Gary Anderson

EXHIBIT 1

CIA 67

Effect of ~~IgG~~ on 'late' onset mice vs Rat Ig. (CIA 58 ref.
22E9. (d28→) (d27→)

7-11 wks OR: Strain: DBA/1 Lac-J

#1-41 . CII:FCA i.d. 100µl MJR #7 died.

#1-41 CII:FCA i.d. 100µl MJR #26 sick → died

Mice scored daily - don't need to do actually

⌐ did need to do as mice come up early

Score all mice. ~~There up by now even if included in~~
~~expt.~~ 34/41 mice up. Use lowest scoring mice, balance b/tn
sample group & control group
~~Mice up from d28→ included in expt~~

Gave 22E9- 0.3mg (110µl) @ 2.65 mg/ml , purifie
i.p. in PBS. from Cell Max beginning Rob
-s/n was pooled ~~& dialysed~~ purified & dialysed i.
PBS. endotoxin = >10pg/ml

        Rat IgG- As for CIA57

Treatment- 0.3mg of Ab i.p. for 10 consecutive days
from d 27 post immunisation. Swollen toes counted

22E9 #1, #9 #14 #16 #18 #21 #22 #30 #31 #38

Rat Ig #15 #20 #24 #27 #33 #34 #35 #36 #37 #40

mice killed on d15 & post initial Ab treatment Blood tak
Rear limbs & spleen fixed.

(NB). Next 22E9 CIA expt. - need to take out
    the lungs of mice given 22E9 and those given control

CIA Practice

Practising collage id. injections in DBA/1 mice and inducing arthritis in these mice.

+ 12 wks.

#2-6 and 8-17 (15 mice) CII:FCA id. 100μL EmmA (2-5 ± 16, Natalie (#6, 8-10, 17), Fiona (# 11-15)
  #1 and #7 died.

#2-5, 8-16 (13 mice) CII:FCA id 100μL
  Emma (#2-5) ~~xxxx~~ Natalie (#8-10, #16) Fiona (# 11-15)
  #6 died , #17 was missing!

Score mice daily - some had come up already, need to score earlier next time.

Kill DBA #10 and #11. (ie #10 scored 10, #11 = 0)
collect blood, and limbs. Do a peritoneal louvage to onah cells by FACS.

Kill remaining mice, collect blood by heart puncture.
collect rear limbs.

No #27

3

CIA 67; 22E9 vs Rat IgG (- #27)

Clinical Score

22 E9 av
Rat IgG av

Day
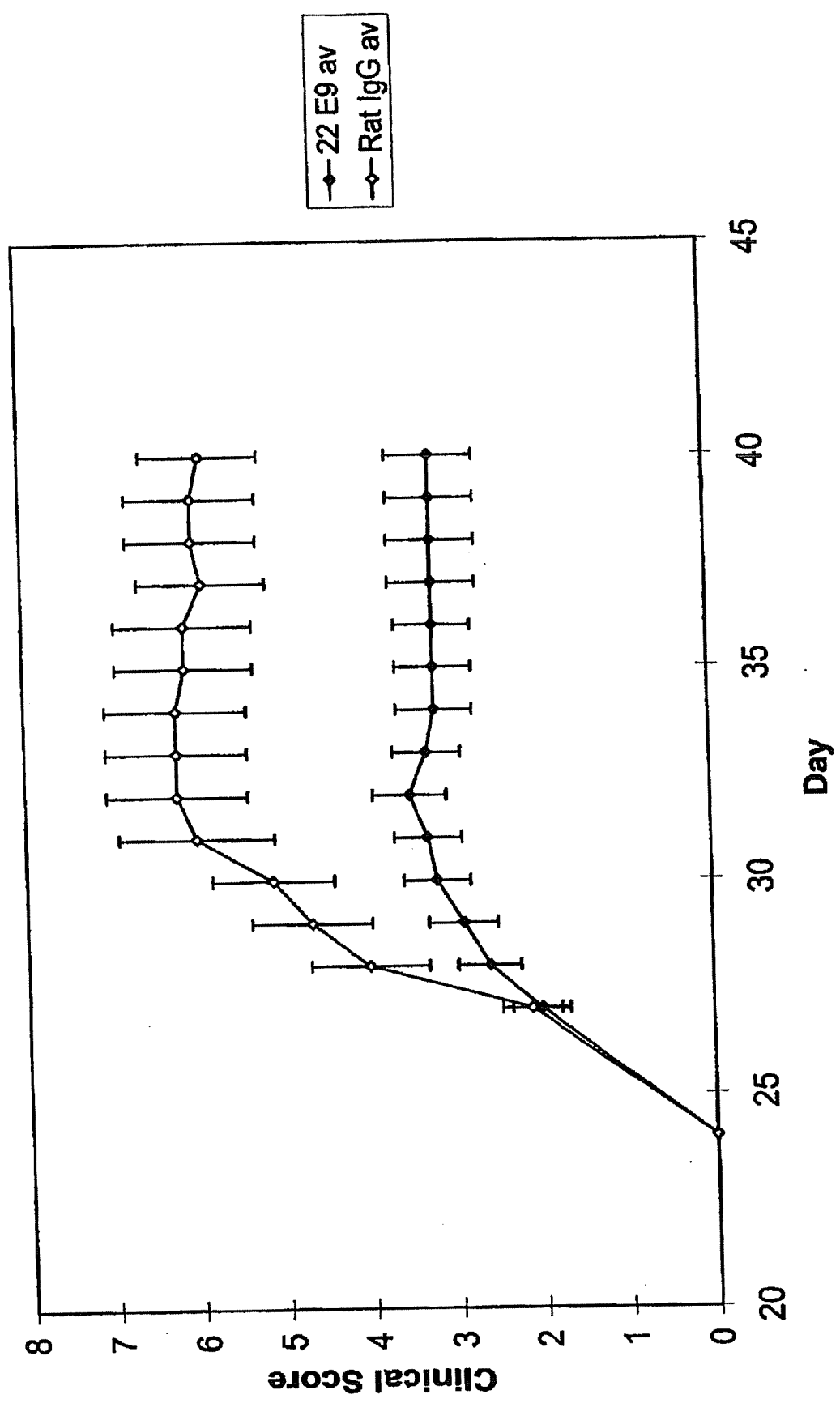
FIGURE 1

EXHIBIT 2

CIA45 – 5AI on established #1

41 ♂ DBA/1 aged 9–13 wks now

— injected c̄ CII/CFA as per usual.
   IKC injected # 1–20
    MR   "   # 21–30
    JD   "   # 31–40

(day 21)

All mice injected c̄ CII boost in CFA (IKC).

(day 27)

Newly +ve mice assigned to one of two injection groups.
(a) 5AI (300μg; i.p.)   ... 10 mice
(b) DX48 (300μg; i.p.)   ... 10 mice
for 10 consecutive daily injections.
   (0.2ml of 1.5mg/ml in PBS)

Mice were p. bled as they received their
.... dose of arthritis.

Mice were sacrificed, bled, spleens & all limbs removed
on their 14th day of arthritis.

N.B. Mouse # 34 was killed on d15 & bled on d19
      # 36   "   "   "   d12
      # 38   "   "   "   d16

CIA-45 ... Day of onset.

ommitted — 26, 26, 26, 26, 26, 26, 26, 24, 26, 24.

SAI — 27, 28, 28, 27, ~~31~~ 29, 29, 30, 29, 27,
28.5 ± 0.4 ~~28.4 ± 0.4~~

DX-48 — 30, 27, 27, 29, 28, 29, 29, 27, 29, 33
28.8 ± 0.6

2

CIA45: clinical scores

PERIOD OF Ab TREATMENT

Days of arthritis

Clinical score

5AI
DX-48
* P < 0.05

3
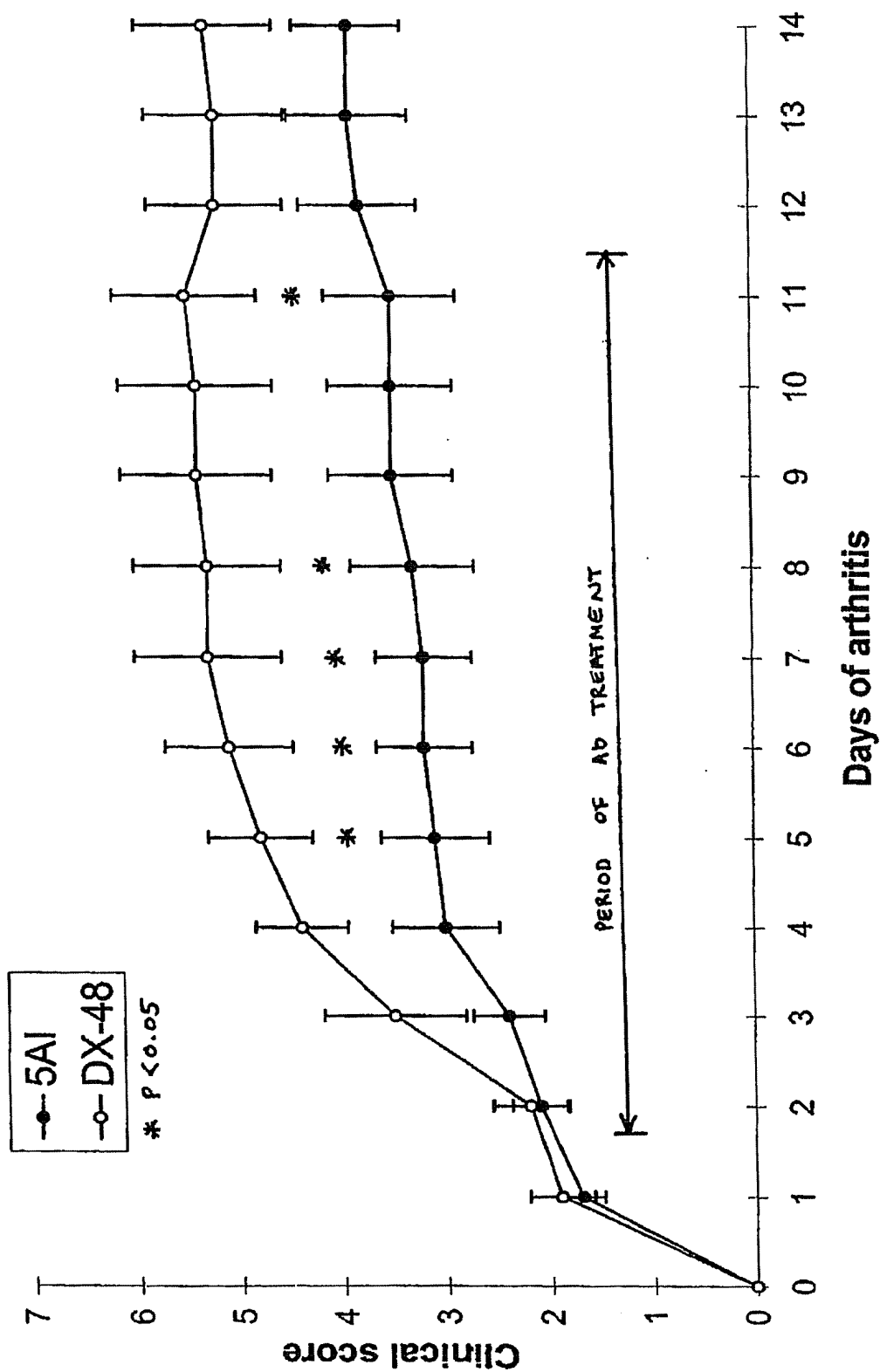
CIA45: mean clinical scores (days2-11)

Mean clinical score

6
5
4
3
2
1
0

P <0.05

5AI   DX-48

Antibody treatment

4

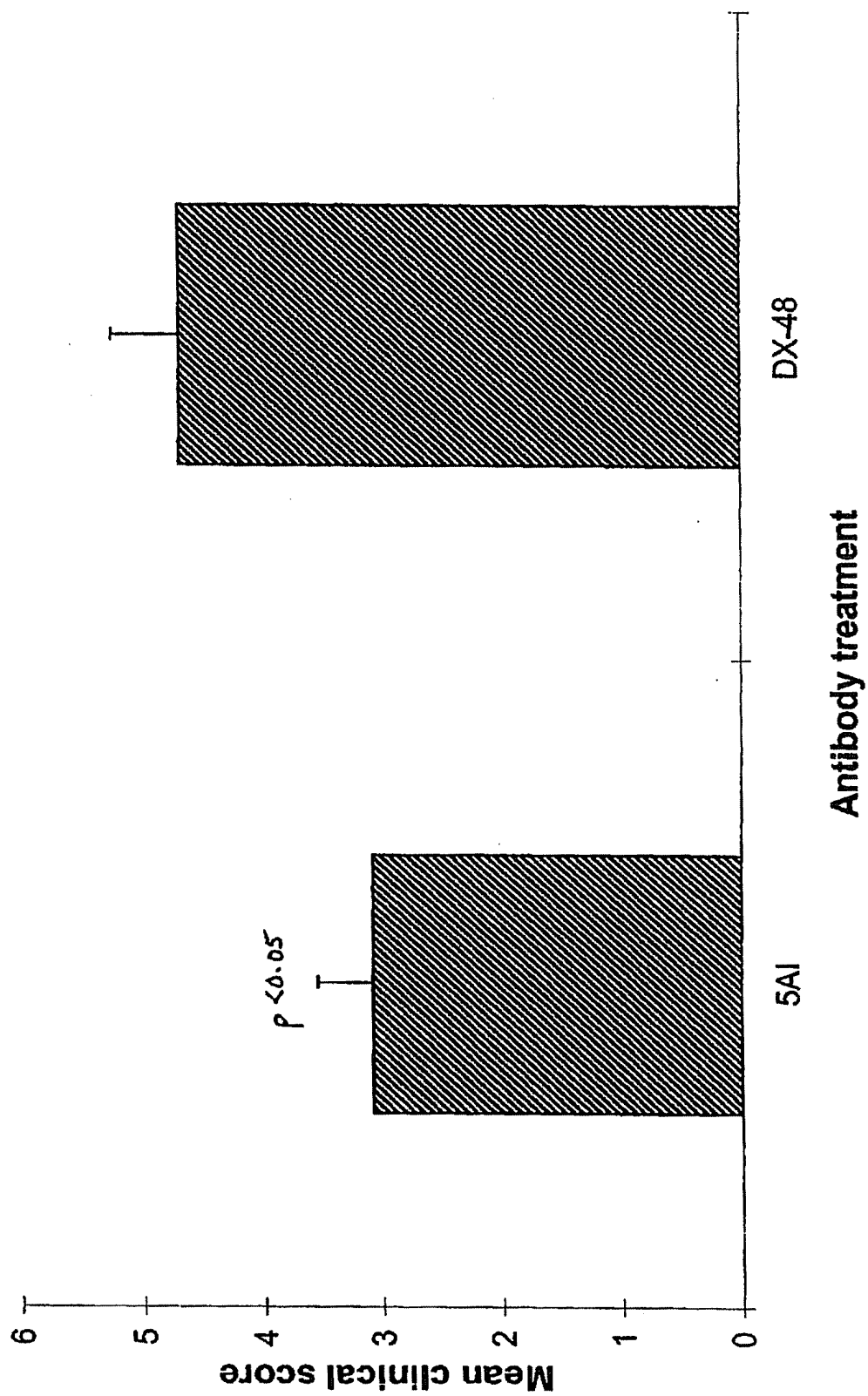| Mouse #	Group	Days... 24	26	27	28	29	30	31	32	3
1		0	0	0	0	0	0	0	0	
2		0	1	1						
3	5AI	0	0	2	2	2	3	3	3	
4		0	0	0	0	0	0	0	0	
5		0	0	0	0	0	0	0	0	
6		0	0	0	0	0	0	0	0	
7	5AI	0	0	0	2	2	2	2	2	
8		0	0	0	0	0	0	0	0	
9	5AI	0	0	0	1	2	3	3	3	
10	5AI	0	0	2	2	2	2	2	2	
11	5AI	0	0	0	0	0	2	2	3	
12		0	2	2	4					
13	DX-48	0	0	0	0	0	2	2	7	
14		0	0	0	0	0	0	0	0	
15	DX-48	0	0	3	4	4	6	6	6	
16	DX-48	0	0	2	2	3	5	5	6	
17	DX-48	0	0	0	0	0	0	0	0	
18		0	1	2						
19	5AI	0	0	0	0	3	3	3	4	
20		0	1	3						
21	5AI	0	0	0	0	2	2	2	2	
22	5AI	0	0	0	0	0	0	1	1	
23		0	2	5						1
24		0	0	0	0	0	0	0	0	
25	DX-48	0	0	0	0	2	2	2	3	
26	5AI	0	0	0	0	1	2	2	1	
27		0	0	0	0	0	0	0	0	
28		0	0	0	0	0	0	0	0	
29		0	1	1						
30	5AI	0	0	2	4	5	7	7	6	
31		0	0	0	0	0	0	0	0	
33		0	1	1						
34	DX-48	0	0	0	1	3	5	5	5	
35		1	3	4						
36	DX-48	0	0	0	0	1	1	1	4	
37	DX-48	0	0	0	0	4	6	6	6	
38	DX-48	0	0	1	1	3	7	7	8	
39		0	2	4						
40		2	4	6						
41	DX-48	0	0	0	0	2	2	2	3	

5

0	31	32	33	34	35	36	37	38	39	40	41
0	0	0.	0								
			7								
3	3	3.	3	4	4	4	3	3	3	3	
0	0	0	0								
0	0	0	1								
0	0	0	0								
2	2	2	2	2	2	3	3	3	4	4	4
0	0	0	0								
3	3	3	3	3	3	3	3	3	3	3	3
2	2	2	3	3	3	3	3	3	3	3	
2	2	3	3	4	4	4	3	3	3	3	4
			9								
2	2	7	6	5	7	6	6	7	7	7	6
0	0	0	0								
6	6	6	7	8	7	7	7	5	6	6	
5	5	6	6	6	6	6	6	6	6	6	
0	0	0	1	1	1	2	2	2	2	2	2
			4								
3	3	4	4	3	3	3	5	5	6	6	6
			7								
2	2	2	2	2	2	2	2	2	2	2	2
1	1	1	1	2	1	1	1	0	0	0	0
			10								
0	0	0	0								
2	2	3	3	3	2	3	3	3	3	3	3.0
2	2	1	3	5	5	5	5	5	5	5	5
0	0	0	0								
0	0	0	0								
			5								
7	7	6	6	7	7	7	7	7	7	7	
0	0	0	0								
			8								
5	5	5	6	6	6	6	6	6	6	6	6
			6								
1	1	4	5	4	6	6	6	6	6	5	
6	6	6	6	6	6	6	6	6	5	6	6
7	7	8	9	9	9	9	9	9	9	9	9
			9								
			7								
2	2	3	3	3	3	2	2	3	5	5	4

6

40	41	42	43	44	45	46
3						
4	4					
3	3					
3						
3	4	5	4			
7	6	6	6			
6						
6						
2	2	1	1	1	1	1
6	6	6				
2	2	2				
0	0	1	1	2		
3	3.0	3.0				
5	5	5				
7						
6	6	6				
5						
6	6	6				
9	9					
5	4	5				

7